REMARKS

Careful consideration has been given to the Official Action of September 6, 2005 and the above amendatory action has been taken to place the application into condition for allowance.

The applicants have carefully studied the outstanding Final Office Action. The applicants respectfully submit that the Examiner's final rejection is based on an incorrect interpretation of the prior art cited. The present response is intended to be fully responsive to all points of final rejection raised by the Examiner, and is believed to place the application in condition for allowance. Furthermore, the applicants submit that the amendments made are of a minor nature, such that a further search should not be required. For these reasons, the applicants therefore respectfully request that this amendment be entered by the Examiner, and request favorable reconsideration and allowance of the application.

Claim amendments

Claims 34 and 35 have been amended by the deletion without prejudice of the use of fluorescence microscopy as one of the methods by which the local refractive index variations are determined. Additionally, claim 35 has been amended to recite equivalent elements and limitations as those of claim 34, to which it is meant to be the equivalent method claim.

Claims 38 and 39 have been amended by the addition of the limitation that an aberrated wavefront is determined for each of the plurality of rays originating from each point in the medium. Support for this amendment is to be found in the specification on page 14, lines 2-7, and in the associated Fig. 5. Concurrently, the limitation to a confocal microscope has been deleted, since the method of imaging rays which are now defined as coming from each point in the medium implies in itself a confocal mode of operation.

The recitation of method claim 40 has been amended to be equivalent to the phraseology and the order of elements used in corresponding apparatus claim 41.

Claim rejections - 35 USC § 112

The Examiner has stated that "Claims 38 and 39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claim 38, which is representative of claim 39, will be exemplified.

Claim 38 requires:

an adaptive optics controller to control an adaptive optical element in a confocal microscope to correct aberrations resulting from variations in the refractive index at a multiplicity of locations in a medium; where

the adaptive optics controller uses an aberrated wavefront determined by the ray tracer.

The entirety of the specification is directed to correcting aberrations resulting from refractive index variations using image processing. For example, refer to figure 2, numeral 34, figure 3, numeral 54 and figure 7. That is, in order to correct the aberrations, a location dependent point spread function is convoluted with an observed image as depicted at figure 3, numeral 54. This is a mathematical manipulation and reconstruction.

However, claim 38 requires a physical, or optical element to be placed in the optical path of a confocal microscope which is adaptive and responsive to the aberrated wavefront (presumably as determined using image processing techniques) to perform the deconvolution step at figure 3, numeral 54. The optical element that performs this deconvolution is not sufficiently described by the specification to enable one skilled in the art to make and use the invention without undue experimentation."

As previously stated in the response filed on February 22, 2005, the applicants respectfully submit that the assertion of the Examiner in the last quoted paragraph is incorrect on two counts. In the first place, the apparatus claimed in claim 38 differs from that claimed in the previous claims in that it is not based on a mathematical manipulation and reconstruction, as asserted by the Examiner. Claim 38 and its base claim 34 do not recite the image processing techniques recited in the previous claims of the parent application to this application, in order to correct the aberrations in the observed image, but rather only the analytical ray tracing without calculating the point spread function and without performing deconvolution. Secondly, instead of the mathematical reconstruction suggested in the earlier claims of the parent application, claim 38 recites the use of an adaptive optical element which is controlled by means of the aberrated wavefront derived from the ray tracing apparatus of claim 34, thereby to correct aberrations resulting from the variations in the refractive index.

Furthermore, as previously stated, the applicants respectfully submit that many kinds of such adaptive optics elements are well known to one of skill in the art, such as are described in the book by R.K. Tyson entitled "Principles of Adaptive Optics", Academic Press, New York, 1991, which is referenced in the Background section of the application.

The Examiner has responded to this submission by explaining that he is not questioning "whether adaptive optics are well known. Rather the question is whether adaptive optics correcting aberrations resulting from variations in the refractive index are known; especially the control of such adaptive optics UTILIZING an "abberated wavefront" derived from tracing "rays". That is, claim 38 requires determining an abberated wavefront from a plurality of traced rays, and then controlling an adaptive optical element utilizing the abberated wavefront to correct for variations in the refractive index of the sample."

In response thereto, the Applicants respectfully submit that the prior art, including Tyson, clearly describes how to control an adaptive optical element to correct the aberrations in an optical system, **when given the wavefront aberrations** that it is desired that the adaptive optical element correct. The major problems in

applications of adaptive optics emerge from the lack of knowledge of the exact wavefront and its phases, and estimations rely on various measurements that are currently the subject of much research and developments in astronomy and other areas. The presently claimed invention shows how to trace rays through the sample causing such wavefront aberrations, and therefrom to determine the phases of the aberrated wavefront. This is the very information which is utilized in the prior art, such as Tyson, to control an adaptive element according to the aberrated wavefront phases and thus to correct these aberrations. Claim 38 therefore recites a novel apparatus for using the ray tracer of claim 34 to determine an aberrated wavefront, which once determined, can be input into any well known adaptive optics element to correct for the aberration itself.

It would appear to the applicants that the Examiner's suggestion that:

> "the question is whether adaptive optics correcting aberrations resulting from variations in the refractive index are known; especially the control of such adaptive optics UTILIZING an "abberated wavefront" derived from tracing "rays""

is akin to suggesting that to show that claim 38 is **enabled**, we have to show that the elements which constitute the very novelty of the claim, already exist in combination in the prior art. The applicants respectfully submit that if this were so, claim 38 would not be enabled, but rather anticipated, or at least obvious !

The present invention discloses a method of measuring the refractive index variations in the sample, from DIC or phase microscopy, and of ray tracing through the sample with varying refractive index, and thus gives the wavefront aberrated phases, and this information is used to set an adaptive element in the manner well known in the art to correct the wavefront and create an aberration-free image.

The adaptive elements may be of any kind of the wavefront correctors which, contrary to the Examiner's assertion, are described in some detail in Tyson, Chapter 6, pages 185-212, such as actively controlled deformable membrane mirrors, segmented mirrors on pistons, spatial light and phase modulators, or any of the numerous adaptive optical devices developed.

In the continuation of his comments, turning to the R.K. Tyson article, the Examiner agrees that "adaptive optics are known. However, the question is what the "known" adaptive optics correct for, and what they are responsive to.

In conclusion of his analysis of what the Tyson reference shows, the Examiner has stated that:

"Tyson DOES NOT teach:

- An adaptive optical element that corrects for variations in the refractive index of the sample; and
- An adaptive optical element that utilizes an abberated wavefront to correct for the variations in the refractive index of the sample.

In order for the applicant to rely upon the Tyson reference as evidence of well known subject matter in support of enablement, Tyson would have to teach at a minimum an adaptive optical element that corrects for variations in the refractive index of the sample."

The applicants respectfully disagree with the above assertion of the Examiner. Claim 38 nowhere recites that the adaptive optics element corrects directly for variations in the refractive index of the sample. Claim 38 recites that the adaptive optical element corrects for the aberrations in the wavefront. The way in which this is performed, by means of applying phase conjugation, is well known in the prior art, such as is explained in detail in Tyson, in Chapter 3, Section 3.1, pages 54-60. The applicants submit that the source of these aberrations - from variations in the refractive index of the sample - is irrelevant to the manner in which the adaptive optical element operates. Thus, for instance, Tyson shows in Fig. 3.5 an aberrating object in the form of a geometrically uniform block with non-uniform structure within it, and it is clear to one of skill in the art that the obvious source of the generation of aberrations during wavefront transmission through the block shown must arise from variations in the refractive index within the block. Such variations are indeed corrected in the image produced, but not by direct actuation of the adaptive optics element from a knowledge of the variations. The latter are only mentioned in the claim to relate the claim to the recitation of parent claim 34.

The applicants therefore respectfully submit that claim 38, and its corresponding method claim 39, are enabled to one of skill in the art, and the applicants therefore request withdrawal of the Examiner's grounds of rejection of claims 38 and 39 under 35 U.S.C. 112, first paragraph.

Claim rejections - 35 USC § 112

The Examiner has stated that "Claims 38 and 39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter which applicant regards as the invention. Both of these claims require a "confocal microscope". However, claims 34 and 35 from which claims 38 and 39 depend, require one of three types of microscopes ("DIC", "phase" or "fluorescence"), none of which are claimed as being "confocal". Therefore, the scope of claims 38 and 39 does not fall within the scopes of the claim from which they depend. Thus it is unclear what type of microscope is actually required by claims 38 and 39."

The applicants have amended claims 38 and 39 by deleting the recitation of the term "confocal". In addition, the applicants have amended the claims by adding the limitation that an aberrated wavefront is determined for **each of** said plurality of rays **originating from each point in said medium**, as shown in Fig. 5 and its associated description on page 14 of the description. The applicants submit that such an imaging arrangement, which is applicable to any of the types of microscope mentioned in claims 34 and 35, is essentially equivalent to a confocal arrangement, such that not only is the scope of claims 38 and 39 unchanged by the amendment, but that they now also fall within the scope of claims 34 and 35.

The applicants therefore request withdrawal of the Examiner's grounds of rejection of claims 38 and 39 under 35 U.S.C. 112, second paragraph.

Claim rejections - 35 USC § 103

Claim 40, which is representative of claim 41, is rejected under 35 U.S.C.

103(a) as being unpatentable over the combination of Goldstein (US 4,827,125 A) and Chan et at. (US 6,275,726 Bl).

The Examiner has stated that:

"Goldstein discloses providing a confocal microscope (figure 1; "confocal... microscope" at column 4, line 37) having an imaging path between a three-dimensional sample (figure 1, numeral 27; "specimen" at column 8, line 6) and its output image plane (figure 1, numeral 35).

Goldstein does not teach:

determining variations of the refractive index in said three-dimensional sample; and

disposing in said imaging path a three-dimensional medium having properties that correct aberrations resulting from said variations of the refractive index in the three-dimensional sample.

Chan teaches imaging a specimen with a confocal microscope ("confocal" at column 2, line 30 and "confocal microscopy" at column 8, line 58), comprising:

determining variations of the refractive index in said three-dimensional sample ("highly light scattering because of the refractive index (n) variations among water and various inter/intra cellular components..." at column 1, lines 25-35); and

disposing in said imaging path a three-dimensional medium ("index matching the cellular components" at column 2, line 37; "replacing inter and/or intrastitial (extracellular) fluid with another (replacement) fluid that has a refractive index more similar to that of the inter/intra cellular components" at column 2, lines 63-66) having properties that correct aberrations resulting from said variations of the refractive index in the three-dimensional sample ("enhancing the visualization of turbid biological tissue comprising the reduction of light reflection and refraction" at column 3, lines 29-31; "improves the imaging of tissues" and "improve the depth of penetration and increases signal to noise values" at column 8, lines 55-57).

It would have been obvious at the time the invention was made to one of ordinary skill in the art to dispose the index matching fluid of Chan into the specimen of Goldstein, in order to enhance "the visualization of turbid biological tissue comprising the reduction of light reflection and refraction" (Chan at column 3, lines

29-31), thereby improving "the imaging of tissues" and "the depth of penetration" and increasing "signal to noise values" (Chan at column 8, lines 55 - 57)."

The applicants respectfully submit that there is a fundamental difference between the invention described in Chan et al, and the claimed invention of the present application. In the Chan et al patent, to the best of the applicants' understanding, there are described "methods of reducing light attenuation in biological media or tissue that include index matching the cellular components of the biological media such that the amount of light reflection and refraction by the tissue is reduced." This is performed according to one embodiment, "by replacing inter and/or intrastitial (extracellular) fluid with another (replacement) fluid that has a refractive index more similar to that of the inter/intra cellular components".

The Chan invention is concerned with matching of refractive indices of the cellular components of the sample with the inter and/or intrastitial (extracellular) fluid in order to improve visibility of the sample. In the Chan et al invention, the variations in the refractive indices are a result of a premeditated act performed using materials of refractive index known in advance in order to affect the visibility of the sample. In contrast to that, in the currently claimed invention, the variations in refractive index are unknown, and are determined by the image information acquirer, which, the applicants respectfully submit, is nowhere shown or suggested in Chan.

The applicants have amended the recitation of claim 40 such that it is now equivalent in structure and element order to its corresponding apparatus claim 41.

Thus, in contrast to what is described in Chan et al, amended claim 40 of the present application now recites:

"A method for confocal microscopy comprising the steps of:

providing a confocal microscope having **an image information acquirer providing information relating to variations in the refractive index** in a three-dimensional imaged volume, said microscope having an imaging path between a three-dimensional sample and said image information acquirer; and

disposing in said imaging path a three-dimensional medium with refractive properties that correct aberrations resulting from said variations of the refractive index in the three-dimensional sample." (Emphasis added.)

The applicants therefore respectfully submit that no combination of Chan et al with any other prior art, whether the Goldstein patent cited by the Examiner, or any other reference, can render amended claim 40 and claim 41 of the present invention as obvious, and the applicants request withdrawal of the grounds of rejection of claims 40 and 41 under 35 USC 103(a).

Claim 34, which is representative of claim 35, is rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Presby (US 4,362,943 A) and Schoen (Ray Tracing Analysis for Media with Nonhomogeneous Indices of Refraction).

The Examiner states that "Presby discloses an information acquirer ("microscopes" a column 3, tine 57) providing information relating to local index variations at any multiplicity of three dimensional locations ("index profile" at column 1, line 57; "refractive index profile" at column 1, line 8) in a medium ("optical fibers" at column 1, line 57); the refractive index variations being determined by fluorescence microscopy ("induced fluorescence" at column 2, line 60; "microscopes are used for ... observing the resulting fluorescence" at column 3, line 58).

While Presby teaches that an "accurate knowledge of the fiber profile is necessary in order to asses the fiber's transmission properties" at column l, line 23, Presby does not teach the additional claimed step of:

a computer employing an analytically determined path of a ray through the multiplicity of 3D locations in the medium, for a plurality of rays impinging thereon in different directions, by utilizing the local variations of the refractive index at the multiplicity of 3D locations.

Schoen teaches:

a computer program ("computer code" in the abstract) employing an analytically determined path of a ray through the multiplicity of 3D locations in a medium, for a plurality of rays impinging thereon in different directions, by utilizing

the local variations of the refractive index at the multiplicity of 3D locations ("to determine ray trajectories in media with spatially varying indices of refractions" in the abstract).

Schoen teaches applications in "fiber-optics" (see the abstract, and section I) for characterizing "the expected system performance" (section I).

It would have been obvious at the time the invention was made to one of ordinary skill in the art to incorporate the ray tracing algorithm of Schoen, utilizing the index profile acquired by Presby and as a final step in the assessing of the "fiber's transmission properties" (Presby, , column 1, line 23), in order to "characterize the expected system performance" (Schoen, section I) thereby ensuring that the fiber optics produced by Presby are manufactured exactly to specification and will perform as expected."

The applicants have amended claims 34 and 35 by the deletion of the use of fluorescence microscopy as one of the methods by which the local refractive index variations are determined. Since the invention in the Presby patent mandates the use of fluorescence measurements, the deletion of fluorescence microscopy from the first element of claims 34 and 35 renders moot the Examiner's citation of Presby.

Furthermore, the applicants have amended claims 34 and 35 by addition of the recitation "determined", to emphasizing that the recited computer utilizes "the **determined** local variations of the refractive index at the multiplicity of three dimensional locations in the medium." (Emphasis added.) The Schoen article indeed describes a method in which ray trajectories are determined in media with spatially varying indices of refraction. However, the spatial variation of the refractive indices described in the Schoen article, is a **predetermined and known** spatial variation, which has to be input to the computer in order to perform the ray tracing methods described in the article.

In contrast thereto, in amended claims 34 and 35 of the present invention, it is recited that the computer utilizes variations of the refractive index in the medium **as determined by** one of the recited microscopy methods, i.e. as measured by the apparatus and methods of the invention, and not as known in advance.

The applicants therefore respectfully submit that no combination of the Presby patent with the Schoen article can render amended claims 34 and 35 of the present invention as obvious, and the applicants request withdrawal of the grounds of rejection of claims 34 and 35 under 35 USC 103(a).

Prior art

The Examiner has made of record prior art, Wolleschensky et al., (U.S. 6,771,417 B1), which is considered pertinent to the applicants' disclosure but is not relied on.

The applicants have carefully studied the Wolleschensky et al., patent, and to the best of their understanding thereof, nothing contained therein affects the patentability of any of the applicants' claims, either alone or in combination with other prior art.

Conclusion

For all of the reasons set forth above, applicants respectfully submit that all of the pending claims 34, 35 and 38-41, as amended where applicable, are believed to be allowable. Withdrawal of the finality of the rejection of this application, entry of this response, and reconsideration and prompt allowance of this application are therefore respectfully requested.

Respectfully submitted,

JULIAN H. COHEN
c/o Ladas & Parry LLP
26 West 61st Street
New York, New York 10023
Reg. No. 20302
Tel. No. (212) 708-1887